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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/469,485
Filing Date: December 22, 1999
Appellant(s): ZHAO ET AL.

Michael D. Yablonsky
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 8, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 8-20.

Contrary to Appellant's statement, claims 1-7 are not cancelled. Claims 1-7 are withdrawn from consideration as not directed to the elected invention, see the Office action of July 7, 2002.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because the summary encompasses limitations that are not present in the claims on appeal.

The invention claimed is drawn to increasing the antigenicity of a recombinant hepatitis B surface antigen (rHBsAg) by filtering rHBsAg from a cell culture, adding a redox buffer,

adjusting the temperature to 34° to 38° C and incubating the recombinant rHBsAg at the adjusted temperature for 40 to 240 hours, see page 5, lines 12-19, page 6, lines 12-26, page 8, line 7 to page 9, line 5.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

In section II, the brief states that claim 19 is "dependent on Claim 8 through Claim 18". However, claim 19 is dependent on claim 18.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 8-20 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

A substantially correct copy of appealed claims 18 and 19 appears on page 2 of the Appendix to the appellant's brief. The minor errors are as follows:

In claim 18, the symbol for degree of temperature, ° , is missing after "34" and "38" of the claim.

In claim 19, the claim was amended to depend from claim 18 in an amendment submitted October 2, 2002.

Claims 8 and 14 contain(s) substantial errors as presented in the Appendix to the brief. Accordingly, claims 8 and 14 have been correctly written in the Appendix to the Examiner's Answer.

(9) Prior Art of Record

4,620,948	BUILDER et al.	11-1986
WO 93/24148	PETRE et al.	12-1993
5,242,812	EVEN-CHEN	9-1993

Valenzuela, P. et al. "Nucleotide sequence of the gene coding for the major protein of hepatitis B virus surface antigen" Nature, vol 280 (Aug 30, 1979), pp. 815-819.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. (US 4,620,948) and Valenzuela et al. (Nature. 1979; 280: 815-819).

The claims are drawn to a method of increasing the antigenicity of a recombinant hepatitis B surface antigen (HBsAg) by obtaining a sterile filtered rHBsAg from cell culture, adding a redox buffer comprising glutathione and oxidative glutathione, incubating the buffer and antigen at a temperature between 34°C to 38°C between 40 to about 240 hours.

Builder et al. emphasize ensuring immunological activity of any protein upon purification. Builder et al. teach inactivity is due to incorrect folding or conformation before or after intracellular precipitation or during the isolation process, see column 1, lines 58-62. The reference exemplifies ways to recover biologically active protein from cell culture by adding a

weak denaturing solution. Builder et al. teach adding 10mM GSH: 1mM GSSG to solubilized protein and incubating the mixture overnight at 37°C to permit the proper refolding into correct disulfide bond formation such as 10mM GSH: 1mM GSSG, and incubating the protein and buffer at 37° C for 24 hours to permit proper refolding (emphasis added). The purified protein exemplified by the method of Builder et al. has a much higher activity than unpurified protein. See column 4, line 61 to column 5, line 2, column 16, lines 28-55, column 17, lines 24-56, column 20, lines 28-57, and examples 13 and 14 in columns 29-30.

Builder et al. does not teach purifying HBsAg. However, Valenzuela et al. establish that immunogenicity of HBsAg of Valenzuela et al. strongly depends on the integrity and proper formation of the disulfide bonds within the antigen, see column 1 on page 348 and the first full paragraph on page 349. Valenzuela et al. also teach that HBsAg particles purified from cell culture are more variable in size than human particles, see the paragraph bridging pages 349-350.

One of ordinary skill in the art at the time the invention was made would have been motivated to purify HBsAg of Valenzuela et al. by the method of Builder et al. to ensure proper folding and antigenicity of the protein from cell culture. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing a properly folded, antigenic HBsAg protein from cell culture using the method of Builder et al. because the isolated, solubilized proteins purified from cell culture by Builder et al. are treated to correct disulfide bridge formation and correct disulfide bridge formation is required for the immunogenicity of a purified HBsAg from cell culture, discussed by Valenzuela et al. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claims 17, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. and Valenzuela et al. as applied to claims 8-16 above, and further in view of Petre et al. (WO 93/24148 A1).

The clams are drawn to adding an aluminum hydroxide adjuvant after the method steps of claim 8 and co-precipitating rHBsAg and the adjuvant.

See the teachings of Builder et al. above. The reference does not teach adding an aluminum hydroxide adjuvant and co-precipitating the antigen and the adjuvant.

However, Petre et al. teaches a method of adsorbing rHBsAg on an aluminum hydroxide adjuvant, see claims 26 and 27.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the rHBsAg purified by the method of Builder et al. and Valenzuela et al. with the aluminum hydroxide adjuvant of Petre et al. to enhance the immunogenicity of the antigen and make an effective vaccine, see claims 1 and 4 of Petre et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because the HBsAg antigen of Builder et al. and Valenzuela et al. would be available in large quantities and the method would ensure that the antigen in properly folded for correct immunologic presentation to the immune system. One of ordinary skill would have had a further reason to expect success because Petre et al. teaches that the vaccine composition comprising the adjuvant and the rHBsAg is stable at 37°C for a week, which is the incubation temperature in the method of purifying rHBsAg in the method of Builder et al. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. and Valenzuela et al. as applied to claims 8-16 above, and further in view of Even-Chen (US 5,242,812).

The claim is drawn to adding formalin and incubating the rHBsAg at 34°C to 38°C for 40 to 72 hours in addition to the method steps of Builder et al.

See the teachings of Builder et al. and Valenzuela et al. above. The references do not teach the method steps of claim 18.

However, Even-Chen teaches that formalin treatment of HBsAg is necessary to make the product safe for human use, see column 3, lines 59-60.

One of ordinary skill in the art at the time the invention was made would have been motivated to formalin-treat the rHBsAg of Builder et al. to render the product safe for human consumption. One of ordinary skill in the art would have had a reasonable expectation for producing the claimed invention because Builder et all teaches a method of purifying antigens with a method to maintain proper folding and Even-Chen teaches that formalin is added after the rHBsAg has been purified. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention as made, absent unexpected results.

(11) Response to Argument

Appellant argues that the starting materials and the end products of the instant method and the method of Builder et al. are different. Appellant states that the starting material of Builder et al. is inactive, insoluble protein and the instant starting material is soluble particles comprising 100 copies of folded rHBsAg protein, lipids and carbohydrates, which is currently

used as a vaccine. Appellant contends that the proteins of Builder et al. are completely denatured protein that is refolded into a biologically active form, while the instant claims start with active proteins existing in protein-lipid particles. Appellant states that in contrast to the method of Builder et al., the instant method results in better defined epitopes within rHBsAg without denaturing and disassembling the lipid complex particles. Appellant also quotes teachings from Builder et al., showing that the design of the reference is to refold insoluble proteins that have been produced as refractile bodies. Appellant also points out that the method steps of Builder et al. require centrifugation in which the supernatant is discarded. Appellant argues that the soluble starting material of the instant invention would be found in the supernatant of Builder et al. that would be discarded. Appellant also asserts that a reasonable expectation of success "for using a redox buffer on a complex protein-lipid particle composed of approximately 100 already biologically active, immunogenic HBsAg proteins" is surprising in view of the prior art.

Regarding the teachings of Valenzuela et al., Appellant argues that the reference only provides motivation to achieve proper folding of recombinant HBsAg and does not cure the deficiencies of Builder et al.

Appellant also compares the teachings in the disclosure and the teachings of Wampler et al., cited in the specification, with the protocol of Builder et al. Appellant concludes from this comparison that the soluble protein instantly claimed would be discarded in the method of Builder et al. because Wampler et al. teach collecting the supernatant. Appellant believes the teachings of Wampler et al. are relevant to the instant claims as prior art for a method of making soluble HBsAg in an attempted, but failed, use of a redox buffer. Appellant asserts that the Examiner simply chooses not to cite Wampler et al. and has not responded to or has

misunderstood Appellant's remarks regarding the reference. Appellant states that instead of using the teachings of Wampler et al., the Examiner cites Valenzuela et al., "- a reference that provides only motivation to obtain a properly folded HBsAg", which is accomplished by Wampler et al. and used as a starting material for the present invention.

Appellant's arguments as well as a review of the prior art cited have been fully considered, but are found unpersuasive. As discussed by Appellant in the paragraph bridging pages 10-11 of the response, the use of the redox buffer by Wampler et al. fails to improve HBsAg. Contrary to Appellant's assertions that the teachings of Wampler et al. have been unaddressed, the Office has explained why the teachings of Wampler et al. are irrelevant to the instant claims. On page 3, lines 4-6 of the Office action mailed May 5, 20003 and again in the last paragraph on page 2 of the Office action mailed November 5, 2003, it is stated that Wampler et al. do not teach the temperature or the length of time of incubation required by steps c) and d) the claims (emphasis added). The instant method step claims require:

a) a soluble sterile filtered rHBsAg purified from a cell culture

b) adding a redox buffer

c) adjusting the temperature to 34° C to 38° C

d) incubating the rHBsAg at 34° C to 38° C for 40 to 240 hours

The method of Wampler et al. provide:

a) a soluble sterile filtered rHBsAg purified from a cell culture

b) adding a redox buffer

Therefore, Wampler et al. teach a completely different method from the method instantly claimed. Not only is the method of Wampler et al. different, it also failed. The following is a quote by Appellant on page 11 of the Appeal Brief of the first full paragraph and the first sentence of the second paragraph:

"Wampler et al. do not teach the claimed method of purifying HBsAg. Wampler et al. do not teach the temperature or the length of time of incubation required by the claims. How can a completely different method, that did not work, provide motivation or a reasonable expectation of success for the instant method?

Appellant agrees." (emphasis added)

Accordingly, it is established that the teachings of Wampler et al. are not germane to the claims presented in the instant application and the reference is not relevant prior art.

In contrast, the method of Builder et al. is relevant prior art. The method of Builder et al. provide:

a) a soluble sterile filtered protein purified from a cell culture, see column 4, line 61 to column 5, line 2, column 20, lines 28-57 as well as working examples 13 and 14

b) adding a redox buffer, such as 10mM GSH: 1mM GSSG to the solubilized protein, see column 16, lines 42-44 and lines 50-53 as well as working examples 13 and 14.

c) adjusting the temperature to 34° C to 38° C, see column 16, line 54

d) incubating the rHBsAg at 34° C to 38° C for 40 to 240 hours, see column 3, lines 34-68 and column 16, lines 53-55.

Therefore, the starting material instantly claimed requires a soluble, sterile filtered rHBsAg purified from a cell culture. The starting material of Builder et al. is also a soluble, sterile filtered protein from a cell culture. Appellant repeatedly argues the differences between the starting material and the method of obtaining the starting material by comparing the teachings of Wampler et al. with the teachings of Builder et al. However, how the starting material is ultimately provided is not a recited element in the claims (emphasis added). In addition, the method steps for obtaining the soluble product is also not recited in the instant claims. The only requirements of the starting material are that the protein is soluble and sterile filtered. Appellant contends that the proteins of Builder et al. are completely denatured and refolded into a biologically active form, while the instant claims start with active proteins existing in protein-lipid particles. However, Appellant is arguing limitations not recited in the claims (emphasis added). The instant claims do not require "complex protein-lipid particle composed of approximately 100 already biologically active, immunogenic HBsAg proteins". The proteins are only required to be soluble and sterile filtered. The denatured proteins of Builder et al. meet the requirements of the claims because they are soluble and sterile filtered, see column 20, lines 43-46 for example.

Therefore, the specific characteristics required by the claims of the starting materials, other than "HBsAg" is identical to the starting material of Builder et al. just before the addition of the redox buffer. The instant claims are drawn to using a redox buffer at a certain temperature for a certain length of time. Builder et al. specifically teach adding 10mM GSH: 1mM GSSG to the solubilized protein and incubating the mixture overnight at 37°C to permit the proper refolding into correct disulfide bond formation, see the previous citations. This is the same

treatment method required for the instantly soluble HBsAg. Builder et al. clearly demonstrate a more than reasonable expectation of success for achieving a properly folded protein with steps claimed by the instant method using the soluble starting materials from cell culture. The only limitation missing from Builder et al. is the purification of HBsAg.

However, as admitted by Appellant, Valenzuela et al. provide motivation for obtaining a properly folded HBsAg antigen.

One of ordinary skill in the art at the time the invention was made would have been motivated to purify HBsAg of Valenzuela et al. by the method of Builder et al. to ensure proper folding and antigenicity of HBsAg from cell culture. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing a properly folded, antigenic HBsAg protein from cell culture using the method of Builder et al. because the isolated, solubilized proteins purified from cell culture by Builder et al. are treated to correct disulfide bridge formation for proper folding and proper linkage between disulfide bonds is required for the immunogenicity of a purified HBsAg from cell culture, discussed by Valenzuela et al.

Therefore, a prima facie case of obviousness has been established. The combined teachings of Builder et al. and Valenzuala et al. teach all of the limitations in the claims, provide a motivation for the ordinary artisan to combine the references and produce the invention with a more than reasonable expectation of success, absent unexpected results to the contrary.

With respect to the rejections regarding claims 17, 19 and 20, Appellant argues that the teachings of Petre et al. do not remedy the deficiencies of the primary references.

In response, there are no deficiencies with the combination of Builder et al. and Valenzuela et al. Therefore, it is maintained that claims 17, 19 and 20 are prima facie obvious in view of the teachings of Builder et al., Valenzuela et al. in further view of Petre et al.

Similarly regarding claim 18, Appellant argues that the deficiencies of Builder et al. and Valenzuela et al. are not remedied by the teachings of Even-Chen.

However, there is no deficiency in the teachings of Builder et al. and Valenzuela et al. for reasons discussed above. Therefore, it is maintained that claim 18 is prima facie obvious in view of the teachings of Builder et al. and Valenzuela et al. in further view Even-Chen.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Shanon Foley
June 12, 2004

Conferees
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Appendix

Recitation of claims 8 and 14 in the amendment submitted October 2, 2002:

8. A method of increasing the antigenicity of recombinant hepatitis B surface antigen (rHBsAg) comprising:

a) providing soluble sterile filtered rHBsAg purified from a cell culture,

b) adding a redox buffer to the rHBsAg.

c) adjusting the temperature to about 34° C to about 38° C,

d) incubating the rHBsAg at about 34° C to about 38° C for about 40 to about 240 hours, wherein the antigenicity of the rHBsAg produced after step d is greater than the antigenicity of

the rHBsAg provided in step a.

14. The method according to Claim 13 wherein the ratio of thiol to disulfide is selected from the group consisting of about 20:1, about 10:1, about 10:4, about 5: 1, about 2:1 and about 1:1.